Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Division of Drug Information at 301-796-3400, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2014 Electronic Submissions

Revision 3

Guidance for Industry

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Additional copies are available from:

Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development Center for Biologics Evaluation and Research Food and Drug Administration 10903 New Hampshire Ave., WO71, Room 4613 Silver Spring, MD 20993 ocod@fda.hhs.gov

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (Tel) 800-835-4709 or 240-402-7800

U.S. Department of Health and Human Services
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Technical specifications associated with this guidance are provided as separate, stand-alone documents and are updated periodically. To make sure you have the most recent versions, check the appropriate center's eCTD web page.

For eCTD and related technical specifications (CBER and CDER): http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ https://www.fda.gov/Developments/ https://www.fda.gov/Developments/ h

For specific documents referenced in this guidance, see the References section at the end of this document.

TABLE OF CONTENTS

I.	INTRODUCTION1
II.	BACKGROUND2
III.	REQUIREMENT TO SUBMIT ELECTRONICALLY UNDER THIS GUIDANCE2
Α.	Types of submissions That Must Adhere to the Electronic Submission Requirement
Des	cribed in This Guidance Document2
В.	Types of Submissions That Are Exempted From the Electronic Submission Requirement
Des	cribed in This Guidance Document3
C.	The eCTD Specifications
D.	Pre-submission Considerations
E.	Submission Structure: Files, Folders, and Granularity
F.	File Formats and Versions5
G.	Transitioning to eCTD Format and Resubmission of Documents5
Н.	Referencing Previously Submitted Documents and Lifecycle
I.	Summary of Clinical Efficacy and Summary of Clinical Safety6
J.	Study Reports and Datasets6
K.	Case Report Forms
L.	Literature References
Μ.	Transmitting Electronic Submissions
N.	FDA Forms
Ο.	Submitting Paper Copies
Р.	Receipt Date7
REFE	RENCE LIST9

Guidance for Industry¹

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product² Applications and Related **Submissions Using the eCTD Specifications**

4 5 6

1

2

3

I. INTRODUCTION

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Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that, at least 24 months after the issuance of a final guidance document in which the Agency has specified the electronic format for submitting certain submission types to the Food and Drug Administration (FDA or the Agency), the content of such submissions must be submitted electronically and in the format specified by FDA.³ This guidance and the technical specification documents it incorporates by reference (see Reference List)⁴ describe how sponsors and applicants must organize the content that they submit to the Agency electronically for all submission types under section 745A(a) of the FD&C Act.

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Therefore, 24 months after this guidance document is finalized, where this guidance document specifies the electronic format for content submitted to the Agency, sponsors and applicants must submit the content to the Agency electronically in the format specified in this guidance document.⁵ Submissions that are not submitted electronically and electronic submissions that

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Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act that issued in February 2014 (745A(a) Implementation Guidance).

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/uc m153574.htm.

(http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292334.pdf). When such additional guidance documents exist, all applicable guidance documents operate in conjunction with each other to provide the format for electronic submission of the type of content described in the additional guidance documents.

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. We update guidances periodically. For the most recent version of a guidance, see FDA's Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

² The term human pharmaceutical products, as used in this guidance, includes those products intended for human use that meet the definition of drug and do not also meet the definition of device under the FD&C Act, including both drugs approved under the FD&C Act and biological products approved under the Public Health Service Act. ³ For additional information on how FDA interprets and intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act, please see the draft guidance for industry *Providing Regulatory*

⁴ To reflect the evolving nature of the technology and the experience of those using this technology, the Electronic Common Technical Document (eCTD) technical specifications are being provided as separate documents that are incorporated by reference into this guidance. These associated specifications will be updated periodically. See the 745A Implementation Guidance for how FDA intends to implement the timetable for these updates. To make sure you have the most recent version of related technical specifications (CDER and CBER), check the eCTD Web page

⁵ This guidance document specifies how certain submission types must be organized for electronic submission to the Agency. For certain types of content, additional requirements for electronic submission of that content type may be provided in a separate guidance document. See, for example, the draft guidance for industry Providing Submissions in Electronic Format — Standardized Study Data that was issued in February 2014.

are not in the format specified in this guidance document will not be filed, unless exempted from the electronic submission requirement.⁶

When finalized, this guidance will supersede the guidance for industry titled *Providing* Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications that was issued in June 2008.

II. BACKGROUND

In section 745A(a) of the FD&C Act, Congress granted explicit authorization to FDA to implement the statutory electronic submission requirements in guidance. Accordingly, as indicated by the use of the words *must* or *required*, this document is not subject to the usual restrictions in FDA's good guidance practice (GGP) regulations, such as the requirement that guidances not establish legally enforceable responsibilities (see 21 CFR 10.115(d); see also the 745A(a) Implementation Guidance).

To comply with the GGP regulations and make sure that regulated entities and the public understand that guidance documents are nonbinding, FDA guidances ordinarily contain standard language explaining that guidance documents should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. FDA is not including this standard language in this guidance document because it is not an accurate description of all of the effects of this guidance document. Insofar as this document specifies the format for electronic submissions, or provides "criteria for . . . exemptions" under section 745A(a) of the FD&C Act, it will have binding effect.

III. REQUIREMENT TO SUBMIT ELECTRONICALLY UNDER THIS GUIDANCE

Twenty-four months after this guidance document is finalized, sponsors and applicants must submit the content for which an electronic format for submission is specified in this guidance document in such electronic format, i.e., such submissions must be consistent with the requirements set forth below.

A. Types of submissions That Must Adhere to the Electronic Submission Requirement Described in This Guidance Document

This guidance document applies to all submission types to which the requirements set forth in section 745A(a) of the FD&C Act apply. For more information on how FDA interprets and

⁶ See section II.B below.

⁷ FDA considers certain *master files* to be submissions to an NDA, ANDA, BLA or IND, and therefore to fall within the scope of the requirements set forth in section 745A(a). See Section III.A of the 745A(a) Implementation Guidance. These include new drug master files (DMF) (21 CFR 314.420), new biological product files (BPF) (21 CFR 601.51) and any amendments/annual reports to previously submitted DMFs or BPFs. FDA will exempt existing master files previously submitted in non-electronic format; these files need not be resubmitted electronically.

intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act, please see the 745A(a) Implementation Guidance.

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B. Types of Submissions That Are Exempted From the Electronic Submission Requirement Described in This Guidance Document

The statute allows FDA to set forth criteria for exemptions from the electronic submission requirements. Accordingly, FDA will exempt the following types of submissions from the requirements set forth in this guidance:

- All submissions regarding devices that are regulated by CBER as biological products under section 351 of the Public Health Service Act (PHS Act), 9
- Noncommercial investigational new drug applications (INDs), ¹⁰ and
- Existing master files previously submitted in non-electronic format.

Although these submissions will be exempt, FDA also accepts their submission electronically as described in this guidance document.

C. The eCTD Specifications

Sponsors and Applicants (you) must submit electronic submissions using the version of eCTD currently in effect. The version of eCTD currently in effect is specified in the Data Standards Catalog (available at

http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls) and is further described in the following technical specification documents:

- the ICH¹¹ *Electronic Common Technical Document Specification*;
- the ICH eCTD Backbone File Specification for Study Tagging Files; and
- the FDA eCTD Backbone Files Specification for Module 1.

Additional technical specification documents are cited throughout this document. These are listed in the Reference List at the end of this guidance document, and may also be found on FDA's eCTD Web page at

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

In organizing content for electronic submission, you must use either the FDA eCTD Backbone Files Specification for Module 1, version 1.3, or the FDA eCTD Backbone Files Specification for Module 1, version 2.3.

⁸ See the 745A(a) Implementation Guidance.

⁹ Devices regulated by CBER as biological products under section 351 of the PHS Act (42 U.S.C. 262) are generally those intended for use in screening donated blood for transfusion-transmissible diseases.

¹⁰ For purposes of this guidance, the term *noncommercial products* refers to products that are not intended to be distributed commercially and includes investigator-sponsored INDs, emergency-use INDs, and treatment INDs.

¹¹ International Conference on Harmonization.

For submitting advertisements and promotional labeling that are subject to section 745A(a) of the FD&C Act, you must only use the FDA *eCTD Backbone Files Specification for Module 1*, version 2.3. In addition, you must submit the promotional labeling to the appropriate application and not mix submissions of advertisements and promotional labeling with submissions containing other types of information.

D. Pre-submission Considerations

Before making the first electronic submission to an application, you must obtain a pre-assigned application number by contacting the appropriate center.

E. Submission Structure: Files, Folders, and Granularity

Files pertaining to each module must be placed in the appropriate folder (e.g., m1 - m5). The terms *folder* and *subfolder*, as used in this guidance, are intended to be synonymous with *directory* and *subdirectory*. The main submission, regional administrative folders, and certain subfolders must have specific names.

You must use only letters, numbers, hyphens, or underscores in the folder and file names and not blank spaces or special characters. When naming folders and files, the length of the entire path must not exceed 230 characters. Empty folders and files must not be included in the submission.

All documents in the electronic submission must be placed in a main submission folder named using a four-digit sequence number (which you must specify) that is unique within the application. The eCTD backbone file for modules 2 to 5 (*index.xml*) for the submission must be placed in this folder along with the checksum file for the eCTD backbone file (*index-md5.txt*). Numbering for each subsequent submission to the same application is described in the FDA technical specification *eCTD Backbone Files Specification for Module 1*. Sequence numbers are used to differentiate between submissions within the same application and need not correspond to the order in which they are received by FDA. It is not necessary for sequence numbers and IND serial numbers to match for submissions to an IND.

Subfolders within each module are required to organize files in a submission. These subfolders must be placed in the sequence number folder (e.g., folder named 0001 for the initial submission to an application). Empty subfolders must not be included. The *util* subfolder is required to organize supporting eCTD technical files in the submission, as described in the ICH M2 technical specification *Electronic Common Technical Document Specification*. Other specific folder names that are compliant with the eCTD version 3.2.2 format can be found in the same document.

Document granularity, or the level for which the submission content is broken out into separate files, must be consistent with the FDA guidance for industry M4 Granularity Annex, *Granularity Document—Annex to M4: Organization of the CTD*, unless otherwise specified in the ICH M2 technical specification *eCTD IWG Question and Answer and Specification Change Request*

144 Document.

With a few exceptions, ¹² the eCTD specification maps Common Technical Document (CTD) headings to XML elements. The specification indicates that each element (heading) is optional, and that multiple document references (eCTD leaf elements) can be created under each heading.

Sponsors and applicants must also follow the FDA eCTD technical specification *Comprehensive Table of Contents Headings and Hierarchy* for the comprehensive listing of headings and hierarchy and a section mapping the headings to their respective regulations. Because this is a comprehensive listing, not all headings are applicable to all submissions or submission types.

A document can be associated with more than one heading. However, the actual electronic file must be provided only once. The ICH M2 technical specification *Electronic Common Technical Document Specification* provides details on how to refer to an electronic file that has already been submitted.

F. File Formats and Versions

Files within an eCTD submission must adhere to the formats and versions specified in the associated FDA technical specification *Specifications for File Format Types Using eCTD Specifications*. Portable Document Format (PDF) files submitted must adhere to the FDA technical specification *Portable Document Format (PDF) Specifications*.

G. Transitioning to eCTD Format and Resubmission of Documents

When transitioning an existing application to eCTD format, you must not resubmit information that was already received in paper or non-eCTD format.

For example, if your original application was submitted in paper and you are now transitioning to eCTD format by submitting a supplement to the application using the eCTD backbone files, you must not submit electronic copies of files and eCTD backbone files for the previously submitted paper files. However, if you are transitioning a paper master file to eCTD, your first eCTD submission will include all previously submitted paper documents. In addition, you must include a document within your submission that lists the files being resubmitted and where they are located in the eCTD table of contents (see section II.H below).

H. Referencing Previously Submitted Documents ¹³ and Lifecycle

If a document was previously submitted in either paper or non-eCTD electronic format, it must be properly referenced. A document detailing previously submitted information that is

¹² For example, in Module 3, lower level headings subordinate to 3.2.P.2 (e.g., 3.2.P.2.1, 3.2.P.2.1.1) are not mapped to an Extensible Markup Language (XML) element. Consequently, leaf element files relating to, for example, 3.2.P.2.1, 3.2.P.2.1.1, must either be submitted as multiple leafs under the parent 3.2.P.2 element (heading) or combined into larger files and submitted at the 3.2.P.2 heading level.

¹³ Previously submitted documents include previously submitted information by reference for master files, marketing applications, and INDs discussed in 21 CFR 312.23(b), 21 CFR 314.50(g)(1), 21 CFR 314.420(b), and 21 CFR 601.51(a).

referenced by the current application must be submitted in section 1.4.4 of the eCTD. In the text of the document, you must include:

• the application or master file number;

• the application type;

• the date of submission (e.g., cover letter date);

the document name;

the page number; and

• the submission identification (e.g., submission serial number, volume number, electronic folder, and file name) of the referenced document.

If a document replaces a document previously submitted with an eCTD backbone file within the same application, you must use the eCTD *replace* operation to indicate this, rather than submitting the file as *new*. You must not indicate that files are *new* if they are in fact replacing files already submitted. If you intend to remove a file, you must use the *delete* operation, and if you are appending information to an existing file, you must use the *append* operation. For instructions, see the ICH M2 technical specification *Electronic Common Technical Document Specification*.

To refer to documents within another application, include the appropriate letters of authorization for cross-reference in Module 1, if applicable (e.g., letters required by 21 CFR 314.420(d)).

I. Summary of Clinical Efficacy and Summary of Clinical Safety

When submitting a Summary of Clinical Efficacy and/or Summary of Clinical Safety, the location of these documents within the eCTD must adhere to the FDA guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.*

J. Study Reports and Datasets

Study data must only be provided in modules 3, 4, or 5 and not in modules 1 or 2. When providing study information in either module 4 or 5, you must include the Study Tagging File (STF) described in the associated ICH M2 technical specification *eCTD Backbone File Specification for Study Tagging Files*. Individual study files must be referenced in an STF using the appropriate STF *file-tag* describing the document's contents.

If a document has been provided in a previous submission (e.g., referencing a previously provided protocol), you must provide an eCTD leaf referencing the earlier file to the protocol and not resubmit the protocol file.

If it is possible that information will be added to the study report over time (e.g., audit information or a publication based on the study), you must provide the study reports as separate documents. New information must be provided as a separate file, rather than replacing the entire study report.

K. Case Report Forms

You must provide an individual subject's complete case report form (CRF) as a single PDF file. If a paper CRF was used in the clinical trial, the electronic CRF must be a scanned image of the paper CRF, including all original entries with all modifications, all addenda, all corrections, all comments, all annotations, and any extemporaneous additions. If electronic data capture was used in the clinical trial, a PDF-generated form or other PDF representing the information (e.g., subject profile) must be submitted. Each CRF must be included with its corresponding clinical study report, and reference in the report's STF, individually tagged as *case-report-forms*. Do not use the eCTD heading 5.3.7 for CRFs.

L. Literature References

Each literature reference must be provided as an individual PDF file, not referenced by an STF.

M. Transmitting Electronic Submissions

The FDA Electronic Submissions Gateway (ESG)¹⁴ enables the secure submission of regulatory information for review and is our preferred method of transmission. For all submissions that are 10 gigabytes (GB) or smaller, you must use the FDA ESG.

For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*.

N. FDA Forms

Electronic submissions must include only FDA fillable forms (e.g., 1571 or 356h) and electronic signatures to enable automated processing of the submission. The FDA forms are available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm. Scanned images of FDA forms will not be accepted.

O. Submitting Paper Copies

When submitting in eCTD format, paper copies of the application, including review copies and desk copies, must not be submitted. The only exception to this is the submission of paper copies of meeting briefing materials, when requested, as described in the FDA guidance for industry Formal Meetings Between the FDA and Sponsors or Applicants.

P. Receipt Date

The receipt date for an electronic submission will be determined only after the submission has passed a technical validation check to ensure that it can be opened, processed, and archived. In the event of a technical rejection, the submitter will receive a notification in their ESG software

¹⁴ Additional information concerning the FDA ESG is available on the Internet at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

inbox. The submitter is responsible for monitoring this inbox to determine whether a submission

has been rejected. Additional information on the validation of electronic submissions is

275	available in the FDA technical specification Specifications for eCTD Validation Criteria.
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277	Additional information on receipt dates for electronic submissions is available in the FDA
278	guidance for industry Providing Regulatory Submissions in Electronic Format — Receipt Dates.
279	
280	Contact Information
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282	For questions related to providing electronic submissions according to the recommendations in
283	this guidance, you should contact the center electronic submission coordinator at
284	esub@fda.hhs.gov for submissions to CDER and esubprep@fda.hhs.gov for submissions to
285	CBER. Specific questions pertaining to the content of applications should be directed to the
286	appropriate review division or office.

288	REFERENCE LIST
289	
290	(References provided in order of first appearance in text)
291 292	Guidance for Industry Providing Regulatory Submissions in Electronic Format – Submissions
292 293 294	Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act
295 296	ICH M2 technical specification, <i>Electronic Common Technical Document Specification</i> (accessible at http://estri.ich.org/eCTD/)
297 298 299 300	ICH M2 technical specification, <i>The eCTD Backbone File Specification for Study Tagging Files</i> (accessible at http://estri.ich.org/STF/)
301 302 303 304	FDA technical specification, <i>eCTD Backbone Files Specification for Module 1</i> (accessible at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)
305 306	FDA guidance for industry, ICH M4 Granularity Annex Granularity Document — Annex to M4: Organization of the CTD (accessible at
307	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)
308 309 310 311	ICH M2 technical specification, eCTD IWG Question and Answer and Specification Change Request Document (accessible at http://estri.ich.org/eCTD/)
311 312 313	FDA technical specification, FDA eCTD Comprehensive Table of Contents Headings and Hierarchy (accessible at
314	http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Electr
315	onicSubmissions/ucm153574.htm)
316 317	FDA technical specification, Specifications for File Format Types Using eCTD Specifications (accessible at
318 319 320	http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)
321 322 323	FDA technical specification, FDA Portable Document Format (PDF) Specifications (accessible at
324 325	http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)
326 327 328	FDA draft guidance for industry, <i>Providing Regulatory Submissions in Electronic Format – Standardized Study Data</i> (accessible at
329	$\underline{http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm})$
330 331 332	FDA guidance for industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (accessible at
333	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

334	
335	FDA technical specification, Transmission Specifications, Specification for Transmitting
336	Electronic Submissions Using eCTD Specifications (accessible at
337	http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Electr
338	onicSubmissions/ucm153574.htm)
339	
340	FDA guidance for industry, Formal Meetings Between the FDA and Sponsors or Applicants
341	(accessible at
342	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)
343	
344	FDA technical specification, eCTD Validation Specifications Web page, Specifications for eCTD
345	Validation Criteria (accessible on the at
346	$\underline{http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Electr}$
347	onicSubmissions/ucm153574.htm)
348	
349	FDA guidance for industry, Providing Regulatory Submissions in Electronic Format — Receipt
350	Dates (accessible at
351	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)